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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,411	KORNOWSKI ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9,12,14-18,31,87,90,94-96 and 103-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-5,7-9,12,15-17 and 31* is/are allowed.

6)☒ Claim(s) *18,87,90,94-96 and 103-105* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response, filed 07/01/2005, amending claims 1, 7-8, 31, 87, 90, 95, 103 and adding new claims 104 and 105. Therefore, claims 1-5, 7-9, 12, 14-18, 31, 87, 90, 94-96 and 103-105 are currently pending and under consideration in this action.

All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections or rejections repeated herein. As new grounds of rejection are set forth that were not necessitated by amendments to the claims, this action is Non-Final.

Claim Objections

Claims 14 is objected to because of the following informalities:

Claim 14 recites the phrase "drug, or protein, gene" which appears to have the conjunction "or" misplaced. The phrase would be grammatically correct if "or" is inserted between "protein" and "gene". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

This is a new ground of rejection necessitated by material changes to the claim. Claim 18 recites the limitation "the composition" which lacks sufficient antecedent support.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 103-105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

This rejection is of record regarding independent claim 103. The same grounds of rejection are equally applicable to new claims 104 and 105 thus are incorporated herein. (See, Office Action, mailed 03/28/2005, pp. 3-6, Rejection No. 2). A response to Applicant's arguments is set forth below. (Infra, Response to Arguments). The rejection of record is repeated herein with some modification to further clarify the grounds of rejection as well as address any relevant amendments.

The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. More particularly, at the time of invention, administration of conditioned culture media into heart or limb tissue of an animal was not routine and entailed certain unpredictability.

Scope/Breadth of the claims. The claims are broad in the sense that they are directed to administration of any growth culture medium containing any factor(s), wherein autologous bone marrow (ABM) aspirate has been grown in said medium, and where the medium is directly

administered to ischemic sites in heart or limb tissue in any subject, so as to promote collateral blood vessel formation. The aspirate is grown under hypoxia, which is broad insofar as the limitation "hypoxia" is undefined (i.e., varying concentrations of CO_2 and O_2). Further, the growth medium comprises an effective amount of GM-CSF, MCP-1, EPAS1 or HIF-1.

Nature of the invention. The invention encompasses promoting collateral blood vessel formation in the heart by administration of growth culture medium into a subject's heart. Thus, the medium must comprise a sufficient concentration of angiogenesis stimulating cytokines, which are endogenously produced by ABM cells. As such, the invention is distinguishable from administering ABMs into ischemic sites, because here, the ABM cells will at least to a certain level, continuously produce a certain profile of angiogenic factors. In other words, CM would comprise a fixed concentration/combination of necessary factors, which may not be sufficiently present to effect collateral blood vessel formation.

State of the Art and Predictability. At the time of invention, administration of ABM cells, let alone ABM conditioned medium (CM) with/without ABMs, was not routine in the art.[1] Currently it is not routine to administer cultured conditioned medium to ischemic tissue in patients. The processes that lead to collateral blood vessel development are *extremely complex*, requiring multiple growth factors interacting in prescribed order and combinations. (e.g., Fuchs et al. J. Am. Coll. Cardiol. 2001; 37: 1726-32, p. 1726, ¶ 1).

As such, there is a high level of unpredictability of results based on the complexity of the physiology for the process of angiogenesis. Given that the intended outcome is based on a multifactorial and complex pathway, there is unpredictability in practicing the claimed method,

[1] The effective filing date of this application is 03/30/1999 (Provisional Application No. 60/126,800).

regarding the CM characteristics. For example, an essential and variable factor is the concentration of a single, or of a combination of several angiogenic factors, as well as the identity of a given combination of said factors, which is necessary to promote collateral blood vessel formation in a given subject.

Along this line of reasoning, it logically follows that additional grounds of unpredictability are attendant with the level or magnitude of ischemia in a given heart or limb tissue (e.g., administering a single batch of a CM to any ischemic tissue in any subject), in conjunction with the physiological differences amongst various patients or subjects. (e.g., mice versus men).

In addition, in regard to direct administration of CM into a target site, relative to essential concentrations necessary to confer collateral blood vessel formation, i.e., dosage response, there would be unpredictability based on the volume or frequency of injections. For example, even if concentrations of one or more endogenously produced/secreted angiogenic factors is determined for a given batch of CM, there remains a level of unpredictability whether the combination or concentration of all the necessary molecules is present to promote angiogenesis or collateral blood vessel formation. In observing *in vitro* CM-induced proliferation of porcine vascular endothelial cells in a dose related manner[2], one study indicates that, "Whether this effect was caused solely by the increased amounts of VEGF and MCP-1 measured or was also contributed to by other, as yet unknown, molecules is uncertain." (Supra, Fuchs et al., 2001, p. 1730, col. 1).

[2] Results that parallel the data presented in the instant specification, at page 14.

In sum, administrating CM directly into a subject to promote collateral blood vessel formation is unpredictable based on the compositions comprised in the CM and the relative complexity of the process leading to blood vessel formation in an animal.

Amount of guidance provided. The only substantial guidance is limited to conditioned medium examined *in vitro* to show cell proliferation (Spec. p. 11, Example 1) or vascular tube formation (Spec. p. 16, Example 3). As such no substantial relevant guidance is provided with respect to in *vivo* unpredictability, such as with respect to utilization of different growth media, determinations of what concentrations of which angiogenic factors are relevant and dosage response as related to varying concentrations of said angiogenic factors. In sum, there is no significant guidance as to *in vivo* administration of conditioned medium to heart or limb tissue in any animal suffering any level of ischemia, utilizing any growth medium in which ABM cells are grown and said growth medium comprising any given concentration of potentially angiogenic factors.

Number of working examples. As noted above, *in vitro* are provided to examine cell proliferation of pig aortic endothelial cells (Example 1). Furthermore, using said endothelial cells and vascular smooth muscle cells in a co-culture technique culture media effectuated endothelial cell tube formation.

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of relevant working examples, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention.

Response to Arguments

Applicant's arguments filed 07/01/2005 (Remarks) have been fully considered but they are not deemed completely persuasive. In summary, Applicant sets forth the following assertions: (1) there are no concerns with adverse outcomes or toxicity in practicing the claimed invention; and (2) the prior and post-filing art teach administration of ABM conditioned medium.

Applicant's first argument is deemed persuasive since as amended, independent claim 103 defines the conditioned medium as one in which *autologous* bone marrow aspirate has been grown. Applicant asserts that extrinsic evidence in the relevant art demonstrates that conditioned medium alone is sufficient to improve collateral blood flow. (Remarks, p. 9, first full paragraph). First, Applicant cites an article that demonstrates direct administration of ABM conditioned medium into ischemic muscle tissue of mice. (citing, Kinnaird et al. 2004 ; 109: 1543-49).

The article is published about five years after the effective filing date of the instant application. As such, the article cannot be utilized for what it teaches to supplement the relevant omissions in the instant specification. Post-filing art is not probative, because "[T]he filing date becomes a date of constructive reduction to practice in determining priority of invention and this should not be the case unless at that time, without waiting for subsequent disclosures, any person skilled in the art could practice the invention from the disclosure of the application. If information to be found only in subsequent publications is needed for such enablement, it cannot be said that the disclosure in the application evidences a completed invention." *In re Glass*, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974).

In any event, it is unclear to what reference Applicant is referring, where Applicant cites that the reference teaches conditioned medium alone is sufficient for angiogenesis, because

Applicant cites "Kinnaird, page 681, col. 2, bottom", but the article spans pages 1543-49 thus page 681 does not exist.

In reviewing the article, it appears CM is collected and analyzed for the presence of VEGF, bFGF, MCP-1 and PIGF. (e.g., p. 1544, col. 1, last ¶ bridging to col. 2). Similar to what is disclosed in the instant specification, the article further examines whether CM has cell proliferation effects *in vitro*. (e.g., p. 1545, col. 2, ¶ 2). Further, the article demonstrates results where media is administered blood flow returned to approximately 50% of nonischemic limb. (e.g., p. 1545, col. 2, ¶ 4; Fig. 4). However, even if the preceding results were admissible (i.e., prior art teaching), which they are not, mice models would not be predictive for all animals, such as humans. Further, hind limb modeling would not necessarily be predictive for heart tissue collateral blood vessel formation. For example, even in the more closely related (to human) porcine model, an increase in myocardial perfusion is not evidenced by an increased number of capillaries or blood vessels. (Supra, Fuchs et al. 2001, p. 1731, last ¶ bridging to col. 2). Further, in the pig model, angiographic assessment may be less predictive, because extracardiac collaterals can account for blood flow (which is used to indirectly measure collateral blood vessel formation). (Id.). It logically follows, that if there are certain doubts about the porcine model that the murine model is even less predictive of results in higher animals. In sum, the cited article is post-filing art thus inadmissible to fill in the gap present in the instant specification so as to meet the enablement requirement.

Applicant also cites Gnecchi et al., which is also post-filing (Nat. Med. 2005; 11:367-8). Therefore, for the foregoing reasons, the teachings thereof are not admissible.

Moreover, Gnecchi et al. utilize a rat heart model, which would not be translatable to higher animals, such as human.

Finally, Applicant cites the Mickel et al. for the proposition that CM is administered to promote collateral blood vessel formation in a porcine model. (Remarks, p. 10, middle; citing Mickel et al. US 2005/0031600, at ¶ 43). The reference teaches that CM is administered as a negative control in assessing cardiogenic differentiation of marrow stromal cells (MSC). Notably, the reference teaches that media alone does not appear to promote collateral blood vessel formation, whereby it is noted that angiogenesis did not occur in control animals (hearts), where myocardial improvement, hence angiogenesis, is measured by ejection fraction and decreased expansion of the infarcted site. (e.g., ¶ 122; See also, ¶¶ 118-120)[3]. In view of the foregoing, this rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

[3] Accordingly, the reference is not anticipatory against claim 103 (Rejection No. 5, Action mailed 03/28/2005).

3. **Claims 87, 90 and 94-95 are rejected under 35 U.S.C. 102(e) as being anticipated by Bauer et al. (US 5,997,860; reference of record; hereinafter the '860 patent).**

This rejection is new insofar as its application to claim 90. The claims are directed to a composition comprising autologous bone marrow aspirate. The limitation "bone marrow aspirate" (BMA) is interpreted to mean aspirate aspirated from an animal. (e.g., Specification, p. 17, last ¶). The limitation is not exclusively defined anywhere in the specification nor further delimited in the claims. Generally a bone marrow aspirate is a small amount of bone marrow that is removed, e.g., through aspiration. Thus, according to such an interpretation the aspirate is not further clarified with respect to subpopulation of cells comprised therein. However, it must be noted that where cells within the aspirate are cultured there is clarification of subpopulation of cells (e.g., adherent or $CD34^+$ bone marrow cells) by virtue of the standard culturing techniques taught in the specification (e.g., p. 12, under "Pig Bone Marrow Culture"; p. 15, Example 2; teaching centrifugation of aspirate, seeding cells obtained therefrom for culturing and washing or replenishing of growth medium). Put another way, the disclosed embodiments that relate to BMA culturing do not support the assertion that BMA is not clarified as to subpopulations of cells.

In sharp contrast to the disclosure, Applicant is of the view that regardless of centrifugation and culturing (e.g., washing and media replacement for 4 weeks) the bone marrow aspirate that is freshly drawn is of the same profile with respect to the subpopulations of cells, as that which is clarified and cultured. In other words, all the claims are limited to aspirate comprising "the full spectrum of bone marrow cells" (Remarks, p. 15, bottom), which interpretation is within the general meaning of bone marrow aspirate.

The limitation of exposure to hypoxia is interpreted as broadly as reasonable in light of a lack of any exclusive definition as to what defines hypoxia, e.g., CO2 concentration. (e.g., Specification, p. 8, indicating oxygen levels of 0.5 to 2.5%). In other words, even if some cells in culture would be exposed to relatively hypoxic conditions as compared to others then the limitation is met (e.g., 5% CO_2 is considered hypoxic).

The limitation "conditioned medium" is interpreted as medium in which bone marrow cells are grown. (e.g., p. 11, last ¶). Furthermore, the limitation directed to exposure to GM-CSF, MCP-1, EPAS1 and HIF-1 is interpreted to mean that said angiogenic factors are present, regardless of from what source. (e.g., endogenously produced/secreted versus exogenously provided).

Limitations directed to an intended use for said BMA are deemed of little moment in distinguishing the claimed composition from a similar composition disclosed in the prior art. In other words, the only relevant claimed structural characteristics are that the composition is BMA (which is certainly autologous as to at least the subject from which it is aspirated).

The '860 patent teaches that 30 ml of fresh bone marrow aspirate (BMA) is obtained from an individual, thereby the BMA is autologous as to the individual from whom it is obtained. (e.g., col. 36, ll. 46-48). Furthermore, the reference teaches that the aspirate can be fractionated or *that whole bone marrow may be used.* (e.g., col. 36, ll. 57-60). The reference teaches that bone marrow cells are cultured, i.e., set up in culture medium. (e.g., col. 36, ll. 61-65).

In addition, the reference teaches that cultures are incubated at 5% CO_2 thus meeting the limitation for hypoxic. (e.g., col. 37, l. 10; claims 87, 94). Furthermore, with respect to the culture comprising at least one angiogenesis cytokine from the recited list of cytokines, it is an

intrinsic property of ABM cells to express said cytokines (e.g., MCP-1 or GM-CSF). Therefore, in effect the reference teaches ABM cells that necessarily comprise at least one of the recited cytokines. As further evidence, knowledge in the prior art clearly demonstrates that MCP-1 is endogenously produced. (See, Cashman et al. Blood, 1998; 92: 2338-44; Abstract; p. 2343, Fig. 1; teaching that MCP-1 is an endogenously produced chemokine)[4].

In addition, Applicant asserts that bone marrow is a natural source of a broad spectrum of cytokines, including colony stimulating factors. (e.g., Specification p. 6, ll. 1-16; p. 7, ll. 10-11; See also, Remarks, filed 07/01/2005, p. 9, last sentence of first full paragraph; p. 15, second full paragraph). Indeed, Applicant explicitly states, "[U]se of the [ABM] cells per se could prove a more sustained sour[ce] of these natural angiogenesis agents". (Remarks, p. 15, middle). In sum, there is evidence present either in the art or by Applicant's admissions that clearly demonstrate that the ABM composition that the '860 patent teaches comprises cells that inherently produce MCP-1. (claims 90, 94, 95). Therefore, the reference anticipates the rejected claims.

4. Claims 87, 90 and 94-96 are rejected under 35 U.S.C. 102(e) as being anticipated by Avraham et al. (US 5,980,893; see whole document; hereinafter the '893 patent).

This is new ground of rejection. The claims are interpreted consonant with what is stated above.

The '893 patent teaches a composition comprising human bone marrow obtained by aspiration, i.e., autologous BMA. (e.g., col. 9, ll. 35-39).

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[4] Normally, only one reference should be used in making a rejection under 35 U.S.C. 102. However, a rejection over multiple references has been held to be proper when the extra references are cited to show that a characteristic not disclosed in the primary reference is inherent (e.g., endogenous expression of MCP-1). *See* MPEP § 2131.01.

Furthermore, the composition can comprise heparin. (e.g., col. 9, l. 39; claim 96). In addition, the aspirate is incubated in culture medium and grown at 5% CO_2. (e.g., col. 9, ll. 45-49; claims 87, 94). In addition, even for the brief time of culturing, the bone marrow cells would inherently (i.e., endogenously) produce MCP-1. (Supra, Cashman, 1998; claims 87, 90, 95). Therefore, the reference anticipates the rejected claims.

Allowable Subject Matter

In view of the foregoing, claims 1-5, 7-9, 12, 15-17 and 31 are allowed. Claim 14 is objected to due to a minor informality, but is otherwise allowable.

Conclusion

Claims 18, 87, 90, 94-96 and 103-105 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday-Friday from 8:30-5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

DANIEL M. SULLIVAN
PATENT EXAMINER